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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

1. ABSTRACT

Title

091301 – FEIBA Global Outcome Study (FEIBA-GO)

Keywords

Activated prothrombin complex concentrate; anti-inhibitor coagulant complex; congenital hemophilia; FEIBA prophylaxis; high-responding inhibitor; post-authorization study; real world evidence

Rationale and background

Hemophilia represents a rare chromosome X-linked genetic disorder of primary hemostasis, which is caused by a deficiency in coagulation factor VIII (FVIII; hemophilia A) or coagulation factor IX (FIX; hemophilia B). Individuals with severe deficiency require life-long coagulation factor replacement therapy for treatment or prevention of spontaneous or traumatic bleeds. One of the most serious complications of replacement therapy is the development of inhibitory antibodies against the exogenously applied coagulation factor in as many as 20% to 30% of patients with severe hemophilia A and in 1% to 5% of patients with severe hemophilia B, resulting in severe and recurrent bleeds in joints, muscles and soft tissues leading to significant joint damage and morbidity. Bypassing agents, anti-inhibitor coagulant complex and recombinant factor FVIIa, can control acute hemorrhages in these patients. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII.

FEIBA-GO was a post-authorization, prospective, uncontrolled, observational, non-interventional, open-label, multicenter cohort study aiming to assess the long-term, real-world effectiveness and safety of FEIBA in congenital hemophilia A or B patients with high-responding inhibitors across routine clinical practice settings.

Research question and objectives

The purpose of the study was to document the natural history of congenital hemophilia A or B disease in patients with high-responding inhibitors either to FVIII or FIX and to describe long-term outcomes in terms of effectiveness, safety and quality of life (QoL) in patients receiving FEIBA in routine clinical practice.

The primary objective was to describe the hemostatic effectiveness of FEIBA in a variety of clinical settings including on-demand therapy, prophylaxis and immune tolerance induction in hemophilia A or B patients with high-responding inhibitors.

The secondary objectives were joint functionality outcomes in routine clinical practice, safety of FEIBA, health-related QoL (HRQoL), acute and chronic pain associated with hemophilia, daily activity level, health resource use, individual pharmacodynamic properties of FEIBA by thrombin generation assay, and FEIBA use in different clinical settings.

Study design

The FEIBA-GO study was a post-authorization, prospective, uncontrolled, observational, non-interventional, open-label, multicenter cohort study. Treatment regimens were prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care was performed as was standard for the site and patient´s healthcare. The study population included approximately 55 male hemophilia A or B patients with high-responding inhibitors who had been prescribed FEIBA for the treatment or prevention of bleeding events by a treating physician prior to the decision to enroll in the study. The patient participation period was 4 years from enrollment to completion.

The study design included a screening visit, interval visits within the individual 4-year observational period (frequency was upon discretion of the investigator but, in general, every year; however, they could have been more frequent) and the End of Study Visit.

Setting

The treating physician determined the treatment regimen, as well as the frequency of laboratory, radiologic and clinical monitoring. Study visits were to coincide with routinely scheduled and emergency visits. Available data from these visits were recorded in the electronic case report forms. The protocol did not require any additional testing or monitoring beyond what was deemed necessary by the treating physician.

Dosage and duration of treatment depended on the severity of the hemostatic disorder, localization and extent of the bleeding and on the clinical condition of the patient. Dosage and frequency of administration were always guided by the clinical efficacy in each individual case. As a general guideline, a dose of 50 to 100 U FEIBA per kg BW was recommended; a single dose of 100 U/kg body weight (BW) and a maximum daily dose of 200 U/kg BW must not have been exceeded unless the severity of bleeding warranted and justified the use of higher doses. The FEIBA treatment regimen was determined by the treating physician.

Patients and study size, including dropouts

Patients were male hemophilia A or B patients with high-responding inhibitors who had been prescribed FEIBA for the treatment or prevention of bleeding events by a treating physician prior to the decision to enroll in the study. No additional diagnostic or monitoring procedures were applied to patients, except those that were part of normal/routine clinical practice.

Variables and data sources

Efficacy endpoints included the following for patients receiving the on-demand regimen and for breakthrough bleeds in patients on prophylaxis: determination of annualized bleeding rate (ABR), including all bleeds and joint bleeds; assessment of effectiveness, including number of treated bleeds and hemostatic efficacy ratings using an "excellent-to-poor" 4-point Likert scale; and FEIBA administration details. Secondary endpoints included joint clinical outcomes assessed by musculoskeletal evaluation of joints, number of total target joints (defined as 3 or more bleeds in the same joint in a 6-month period), number and reason of invasive surgical procedures, number of breakthrough bleeding events in patients on prophylaxis and number of consecutive months on prophylaxis. Additional assessments included HRQoL, pain assessments daily activity levels and health resource use. Safety endpoints included adverse events (AEs) and serious AEs.

Results

Study participants

The trial enrolled patients at 26 trial sites in 11 European countries. The first patient entered the study on 03 September 2014, and the last patient left the study on 28 February 2020 when the sponsor terminated the study due to non-feasibility of reaching the targeted patient number and achieving the planned length of clinical observation for the patients enrolled.

A total of 51 patients were screened. There were no screening failures. One patient was lost to follow-up; this patient was excluded from the safety analysis set. The follow-up duration was at least 6 months in 45 patients (88.2%), 12 months in 39 patients (76.5%), 18 months in 26 patients (51.0%), 24 months in 24 patients (47.1%), 36 months in 15 patients (29.4%), and 48 months in 7 patients (13.7%). In total, study discontinuations occurred in 27 patients on the prophylaxis regimen and 7 patients on the on-demand regimen.

The study population was male and included patients with a median age of 16.5 years at baseline (range: 2 to 71 years). It was well balanced across the age groups with 17 children, 11 adolescents, 7 young adults, 13 adults, and 2 elderly patients. Most patients receiving the prophylaxis regimen were below 18 years old, while most patients receiving the on-demand regimen were adults aged 30 years or older. The general medical history was similar between treatment regimens. Forty-nine patients (98.0%) had hemophilia A, and 1 patient (2.0%) had hemophilia B. Hemophilia was severe in all patients. The median time since diagnosis was 14.31 years in the group receiving prophylaxis at screening and 35.42 years in the group receiving on-demand treatment at screening. All patients had documented prior therapies with FEIBA, with a median duration of 14.09 months (range: 0.4 to 188.3 months).

Before screening, FVIII inhibitor titers were documented in 44 patients: 68.2% had high titers (≥5 BU/mL) and 31.8% had low titers (0.6 to <5 BU/mL). Historical FIX inhibitor titers were documented in 1 patient; this patient had a high titer (≥5 BU/mL).

Key results

The percentage of patients with any bleeds and the specific bleeding categories analyzed (treated, spontaneous, injury/traumatic and undetermined cause) were similar between the prophylaxis and on-demand regimens. No trends over time were notable for any of the treatment regimens. Overall, patients using the on-demand regimen had more bleeds (median, 13.0 bleeds; range: 0 to 115 bleeds) than patients using the prophylaxis regimen (median, 4.0 bleeds; range: 0 to 177 bleeds).

The overall ABR was on average lower in patients receiving the prophylaxis regimen (median, 3.41; range: 0 to 58.2 bleeds) than in patients receiving the on-demand regimen (median, 7.58; range: 0 to 29.0 bleeds). The proportion of patients with more than 6 bleeds per year was lower with the prophylaxis regimen (32.4%) than with the on-demand regimen (50.0%). In patients with more than 2 years of study follow-up, the median ABR was 4.8 (n=17, range: 0 to 44.1) for prophylaxis and 3.3 (n=7, range: 0 to 28.4) for the on-demand regimen. In patients with more than 4 years of study follow-up, the median ABR was 1.5 (n=5, range: 0 to 44.1) for prophylaxis and 17.2 (n=2, range: 5.9 to 28.4) for the on-demand regimen.

Overall, by event count, 159 treatment-emergent AEs (TEAEs) and 43 serious TEAEs were reported in 28 of 40 patients (70.0%) and 17 of 40 patients (42.5%) receiving prophylaxis, respectively. These included 9 study drug-related TEAEs in 4 patients and 1 study drug-related serious TEAE (acute myocardial infarction due to coronary artery embolism, which was classified as a thromboembolic event). Thirty TEAEs and 9 serious TEAEs were reported in 10 of 13 patients (76.9%) and 5 of 13 patients (38.5%) who received on-demand regimen, respectively, of which 1 TEAE and 0 serious TEAEs were study drug related.

Discussion

Due to the observational nature of the study, the results rely on data collected in routine practice. Individual bleed information, treatment details and laboratory measures were not always available; consequently, information on the nature of the bleeds (spontaneous or traumatic) was missing for many of the events, as generally occurs in real-world studies.

A high discontinuation rate was observed in this study with only a small number of patients (n=7) completing the 4-year observational period. This was partially due to difficulties to follow-up at regular visits, especially if patients moved from pediatric to adult centers or switched between centers during the study duration.

Poor data quality, including the lack of secondary endpoint data (including QoL, pain and joint assessments), illustrates how difficult it is to obtain these data in clinical practice due to patient/physician time constraints and the complexities and number of the questionnaires applied.

The study was terminated prematurely due to non-feasibility of reaching the targeted patient number and achieving the planned length of clinical observation for the patients enrolled. The final analysis supports findings from previous studies and shows the long-term effectiveness and safety of FEIBA in patients in real-world settings. The study confirmed existing challenges of conducting real-world studies, the place of FEIBA in the non-replacement era, as well as the definition of prophylaxis therapy in clinical practice.

Marketing authorization holder(s)

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*Baxalta is now part of Shire (Shire, a wholly-owned subsidiary of Takeda Development Center Americas)

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